REMARKS

The provisional double patenting rejection of claims 1-6 and 9-24 as claiming the same invention as that of claims 1-22 of co-pending application Serial No. 10/659,195, is respectfully traversed.

The co-pending application Serial No. 10/659,195 was abandoned effective December 22, 2006 and, as such, this rejection is moot and should be withdrawn.

The rejection of claims 7-8 based on obviousness-type double patenting over claim 1 of application Serial No. 10/659,195 is also now moot and should be withdrawn.

The rejection of claims 1-24 on the grounds of non-statutory obviousness type double patenting over claims 1-26 of co-pending application Serial No. 10/535,232 is respectfully traversed. The claims 1-24 of the subject application are patentably distinct from the claimed subject matter of claims 1-26 of copending application Serial No. 10/535,232 because they are directed to a protein conjugate comprising one whole immunoglobulin molecule, while those of U.S.S.N. 10/535,232 are directed to a protein conjugate comprising an immunoglobulin Fc fragment.

It is well known in the art that proteins may have different properties depending on their sizes and 3-dimentional structures.

Accordingly, the Examiner's rejection of claims 1-24 based on obviousness type double patenting should be withdrawn.

I. Claim Rejections Under- 35 U.S.C. § 102

The rejection of claims 1-9 and 11-18 of the subject application under 35 U.S.C. § 102(e) as being anticipated by Heavner (US 2003/0211078); and the rejection of claims 1-2, 9-10, 18-20 and 22, under 35 U.S.C. § 102(e) as being anticipated by Mohamed et al. (US 2006/0153839), is respectfully traversed.

2. Distinctive Feature of the Present Invention

The present invention as described in the amended claims 1-24 is directed to "a protein conjugate comprising i) a physiologically active polypeptide excluding an immunoglobulin and a fragment thereof, ii) a non-peptidic polymer, and iii) an immunoglobulin, which are covalently linked to one another, and having a prolonged in vivo half-life of the physiologically active polypeptide" and a method for the preparation thereof.

The gist of the present invention is based upon the discovery that *in vivo* half-life of a physiologically active polypeptide significantly increases when it is conjugated to one whole immunoglobulin molecule through a non-peptidic linker.

2. Comparison with the References cited by the Examiner

Heavner (US 2003/0211078) discloses a pseudo-antibody comprising an organic moiety covalently coupled to at least two target-binding moieties, wherein

the target-binding moieties are selected from the group consisting of a protein, a peptide, a peptidomimetic, and a non-peptide molecule that binds to a specific targeted biological molecule.

The major objective of Heavner's invention is to enhance the avidity of an antibody by covalently coupling at least two, preferably, more than three, identical target-binding moieties such as a fragment of immunoglobulin (e.g., Fab, Fab') to an organic moiety. Heavner also suggests that the circulating-half-lives of the pseudo-antibodies can be increased by increasing molecular size, but does not provide any specific examples or experimental data supporting such description.

In the Examples of Heavener, various pseudo-antibodies that have two or more Fab fragments of antibodies are identified as target-binding moieties for providing specific binding to multiple compounds. Further, Heavner discloses in Tables 1 to 4 a variety of biological molecules, but such molecules are exemplified only as a source of the target-binding moiety of the pseudo-antibody and no specific embodiment of a conjugate containing the biological molecule itself is provided in the cited reference. Heavner does not disclose a protein conjugate comprising i) a physiologically active polypeptide excluding an immunoglobulin and a fragment thereof, ii) a non-peptidic polymer, and iii) an immunoglobulin, which are covalently linked to one another, and having a prolonged *in vivo* half-life of the physiologically active polypeptide. Moreover, Heavner's conjugate is different from the protein

conjugate as now claimed in the subject application in which an immunoglobulin and a fragment thereof are excluded.

In addition, Heavner does not teach or suggest the possibility of significantly increasing the *in vivo* half-life of the physiologically active polypeptide other than an antibody and a fragment thereof by conjugating one whole immunoglobulin molecule to the physiologically active polypeptide through a non-peptidic linker.

The cited reference, Mohamed et al. (US 2006/0153839) disclose a bispecific molecule comprising: (a) a first recognition binding moiety that binds a C3b-like receptor; and (b) one or more second recognition binding moieties that binds a molecule; said molecule being other than a C3b-like receptor; wherein said first recognition binding moiety is cross-linked via a PEG linker to the second recognition binding moieties; and methods of producing such bispecific molecules. Mohamed et al. provide specific embodiments wherein both of the first recognition binding moiety and the second recognition moiety are antibodies.

Mohamed et al. is directed to providing a bispecific molecule that binds a C3b-like receptor and a molecule other than the C3b-like receptor. Such bispecific molecule binds a molecule such as an antigen of a pathogen and toxin which is desired to be cleared from the circulation in a mammal. However, Mohamed et al. is totally silent regarding the technical problem of the present invention, i.e., significantly increasing the *in vivo* half-life of a physiologically active polypeptide by

conjugating one whole immunoglobulin molecule to the physiologically active polypeptide through a non-peptidic linker.

Further, Mohamed et al. does not disclose a protein conjugate as claimed comprising i) a physiologically active polypeptide excluding an immunoglobulin and a fragment thereof, ii) a non-peptidic polymer, and iii) an immunoglobulin, which are covalently linked to one another, and having a prolonged *in vivo* half-life of the physiologically active polypeptide.

The Examiner's attention is directed to the fact that the protein conjugate of the present invention shows a dramatically increased *in vivo* half-life of the physiologically active polypeptide contained therein and none of the cited references does not disclose such surprising effect. Specifically, the present protein conjugate (physiologically active polypeptide-non-peptidic linker-immunoglobulin) exhibits a significantly increased mean residence time (MRT) which is up to 60-fold higher than that of corresponding free physiologically active polypeptides, polypeptide-PEG conjugate or polypeptide-PEG-albumin conjugates (see Tables 3 to 7 of the subject application).

Accordingly, the protein conjugate of the present invention is different from conjugates taught in the cited references in terms of constitution and effect. As such, the present invention is novel and the rejection under 35 USC 102 of claims 1-24 should be withdrawn.

With regard to the specific rejection of claims 18-20 and 22, the Examiner's attention is directed to the fact that claim 18 has been amended to incorporate the limitations of claim 21, the novelty of which has been acknowledged by the Examiner.

In view of the foregoing, the rejections under 35 USC 102(e) should be withdrawn.

II. Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 18-19 and 23-24 of the subject application under 35 U.S.C. § 103(a) as being unpatentable over Mohamed et al. (US 2006/0153839) in view of Rosen et al. (US 2004/0115165).

As indicated above, claim 18 has been amended to incorporate the limitations of claim 21 whose inventiveness has been acknowledged by the Examiner. Accordingly, it is believed that the Examiner's 103(a) rejection of claim 18 and claims 19, 23 and 24, which depend from claim 18, should be withdrawn.

Reconsideration and allowance of claims 1-24 is respectfully solicited.

Respectfully submitted
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CERTIFICATE OF MAILING

I hereby certify that this Amendment is being submitted to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 via EFS-Web on March 21, 2007.

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